PATENT SPECIFICATION

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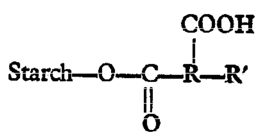
(54) STABILIZED POWDERS

(71) We, F. HOFFMANN-LA ROCHE & CO., AKTIENGESELLSCHAFT, a Swiss Company of 124—184 Grenzacherstrasse, Basle, Switzerland, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to stabilized powders. More particularly, the invention is concerned with stable, dry, free-flowing vitamin B_{12} compositions and a process for the manufacture thereof.

The stable, dry, free-flowing vitamin B_{12} compositions provided by this invention comprise fine particulate vitamin B_{12} coated with a water-soluble, food grade starch derivative of the general formula



(I)

wherein R represents a R′-substituted dimethylene or trimethylene group and R′ represents a hydrophobic group selected from alkyl, alkenyl, aralkyl and aralkenyl groups containing from 5 to 18 carbon atoms.

It has long been recognized in the pharmaceutical field that vitamin B_{12} is unstable under certain conditions and in the presence of certain other essential vitamins such as, for example, thiamine and, most notably, ascorbic acid. In addition, other substances which may be present in vitamin-containing preparations such as, for example, reducing sugars may also have a deleterious effect on vitamin B_{12}. There have been numerous attempts to stabilize vitamin B_{12} both in solution and in dry form. The present invention is concerned with the latter aspect of the problem of stabilizing vitamin B_{12}.

There are several powder or dry forms of vitamin B_{12} commercially available at the present time. An example of such a product is an adsorbate of vitamin B_{12} on a cation ion-exchange resin such as described in United States Patent No. 2,830,933. Such adsorbates, although being relatively stable, have the disadvantage of being expensive to prepare. Further, there exists the possibility that, due to the binding power of the adsorbate, uniform dissociation thereof to release vitamin B_{12} may not occur under all conditions in the gut.

In a further commercial preparation in dry form, vitamin B_{12} is dispersed in a gelatin matrix. This product is prepared by forming an aqueous solution of vitamin B_{12} and gelatin, freezing it into thin sheets and comminuting the sheets into fine particles. Such particles, by the nature of their formation, (i.e. the fragmentation of the sheets of frozen gelatin solution) must contain a certain small percentage of exposed vitamin B_{12}. The exposure of some vitamin B_{12} in this product will unavoidably result in some degradation under conditions where degradation would normally occur. In addition, this product, by virtue of its gelatin content, is not amenable to rabbinical certification thereby precluding its use in kosher foods.

Still another commercial product in a dry form containing vitamin B_{12} comprises an intimate admixture thereof with mannitol. This product has the advantages of being amenable to rabbinical certification and of being relatively inexpensive. However, as this product is only an admixture wherein vitamin B_{12} does not have a uniform protective coating, it suffers the major disadvantage of being very unstable in comparison to the products described earlier.

It is therefore apparent from a consideration of the commercial products described hereinbefore that a dry form of vitamin B_{12}, which is free from all the aforementioned disadvantages and which possesses excellent handling and dispersing characteristics, would readily be accepted by both the food and pharmaceutical industries. Such a product is provided in accordance with the present invention.

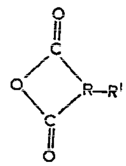
In accordance with the present invention,

vitamin B_{12} is provided in a stable, dry form which possesses outstanding handling and dispersing characteristics.

The process for the manufacture of the present vitamin B_{12} compositions comprises spray-drying an aqueous solution of vitamin B_{12} and a water-soluble, food grade starch derivative of formula I hereinbefore.

The food grade starch derivative which is used in the present invention has been modified to contain both a hydrophobic and a hydrophilic group. In particular, the modified food grade starch derivative used in the present invention to form a protective matrix over particles of vitamin B_{12} is a water-soluble starch acid-ester of a substituted dicarboxylic acid (i.e. succinic or glutaric acid) of formula I.

The preferred starch derivative is derived from succinic acid. These starch derivatives are prepared by reacting food grade starch in an alkaline medium with a substituted cyclic dicarboxylic acid anhydride of the general formula



(II)

wherein R and R′ have the significance given earlier.

Further details relating to the preparation of the starch derivatives may be found in United States Patent No. 2,661,349.

The hydrophilic group of the food grade starch derivative is the free carboxyl group, whereas the hydrophobic group is the group denoted by R′. The substituent on the starch molecule therefore imparts thereto both hydrophobic and hydrophilic properties. It will also be appreciated that, while the starch derivatives described hereinbefore can be prepared using most commercial starches, only those starches recognized as food grade are contemplated within the scope of the present invention because of the intended uses of the products formed therewith.

The stable vitamin B_{12} microbeadlets provided by the present invention can be formed using conventional spray-drying techniques and equipment. It is preferred, however, to form them by a novel spray-drying technique wherein, during the spray-drying operation, the droplets of aqueous solution of vitamin B_{12} and starch derivative are contacted in the drying chamber with a powder spray of an ultrafine (i.e. 2—15 microns) absorbent. Examples of suitable absorbents include silicic acid, silicon dioxide, alkali metal silicates, magnesium carbonate, kaolin clays, dicalcium phosphate, tricalcium phosphate or any similar material. Such materials must meet a number of criteria, that is to say, they must be substantially insoluble in cold water, resistant to wetting by water, possess the capability to absorb and/or absorb water and oil, be free-flowing and resistant to the development of static electricity. Preferably a sufficient amount of absorbent is added to constitute from 1% to 5% by weight of the dry, free-flowing composition.

In the preferred spray-drying operation, the absorbent is metred directly into the spray-drying chamber, thereby coating the semi-dried droplets of product. The absorbent prevents the build-up of material on the chamber wall, minimizes the development of static electricity during the operation and prevents the deleterious formation of large masses of wet product. Alternatively, the absorbent can be admixed with product which has previously been spray-dried by conventional procedures prior to introduction into the spray-drying chamber. The presence of particles of previously spray-dried product, which act as seed particles, facilitates the formation of large dried agglomerates of particles which are individually uniformly coated. In either case, the product is stable, free-flowing microbeadlets, which may be present singly or as agglomerates of individual beadlets. The stable, dry products contain from 0.05% to 5% by weight, preferably about 0.1% by weight, of vitamin B_{12}. The product formed by this improved spray-drying operation is a dense, heavy material and thereby superior to the light, fluffy powder products which are prepared by conventional spray-drying techniques. Because of its excellent dispersibility, the dry vitamin B_{12} preparation of the present invention is ideally suited both for incorporation into food premixes and powder blends such as tablet granulations. In addition, tablet granulations formed therewith are advantageously amenable to the production of tablets by direct compression.

In addition to the aforementioned starch derivative and vitamin B_{12}, the solution to be spray-dried in accordance with the invention preferably contains preservatives, for example, sorbic acid, sodium benzoate, methyl *p*-hydroxybenzoate and propyl *p*-hydroxybenzoate, as well as a suitable buffering agent. A sufficient amount of a buffering agent, preferably a buffer pair, for example, citric acid and sodium citrate, is used to buffer the pH of the microbeadlets to between pH 4.0 and 4.6, preferably to about pH 4.2. The buffering of the microbeadlets to such a pH enhances the stability thereof in the presence of substances such as ascorbic acid.

The stable, dry vitamin B_{12} compositions of the present invention may be used in the production of vitamin tablets containing vitamin B_{12} alone or vitamin B_{12} in combination with one or more other vitamins, minerals

and other nutrients such as are conventional in multivitamin preparations. In addition, the excellent uniformity with which the products of the present invention disperse in powder blends makes them ideally suited for the production of dry powder premixes for the fortification of foods, for example, breads, cereals, baked goods and puddings and for the production of powder premixes suitable for the fortification of dry materials e.g. animal feeds.

A preferred stable, free-flowing vitamin B_{12} powder composition according to the present invention comprises, by weight, about 0.1% of vitamin B_{12}, about 0.1% of sorbic acid, about 0.2% of sodium benzoate, about 10% of a citric acid/sodium citrate buffer sufficient to buffer the pH of said composition to between pH 4.2 and 4.4, from 2% to 3% of silicic acid and, as the remainder, a water-soluble food grade starch derivative of formula (I) in which R represents a substituted dimethylene group.

The following Examples illustrate the present invention:

Example 1.

A stable, dry vitamin B_{12} composition is prepared from the following formulation:

Ingredient	Quantity in grams
Starch acid/ester of 1-octenyl succinic acid	1,000.00
Sodium citrate	60.00
Citric acid	40.00
Sodium benzoate	2.00
Sorbic acid	1.00
Cyanocobalamin (15% excess based on actual assay)	1.15
Purified water	2,500.00

* Capsul, National Starch and Chemical Corp., New York, New York.

1 litre of purified water is heated to a temperature of about 70°C and the sodium benzoate, sorbic acid, sodium citrate and citric acid are dissolved therein with stirring. To this solution is slowly added the starch derivative and stirring is continued at constant temperature until solution is complete. The solution, which is initially highly aerated, is allowed to stand until it becomes clear. The pH is adjusted to a pH of about 4.3 using the citric acid/sodium citrate buffer.

A second solution is prepared by dissolving the cyano-cobalamin in 100 ml of purified water which has been heated to about 70°C. This solution is then added with stirring to the first solution followed by sufficient water, heated to about 70°C. to yield a final volume of 2500 ml.

The inlet temperature of a 4.26 m Bowen Dryer is adjusted to 182°—190°C and the outlet temperature to 94°—104°C. The operation of the spray-drier is started using water. After the system is well balanced, the water is shut off and the cyanocobalamin solution fed into the dryer. The atomizer wheel positioned below the inlet of the absorbent material rotates at a speed of 10,000 to 12,000 revolutions per minute. The silicic acid glidant (absorbent) is metred into the top of the dryer at a concentration of about 2—3% based on the weight of the spray-dried product. The wet, agglomerated spherical particles are thereby coated prior to impinging on the drying chamber wall. As the particles do not adhere to the chamber wall or form large wet agglomerates, a long drying period is assured.

In operation, it is necessary from time to time to make certain adjustments in the drying conditions to optimise the physical properties (e.g. density and particle size distribution) of the agglomerated spray-dried product.

The resulting material is a fine, pink, free-flowing powder having a moisture content of from about 1% to 3% by weight and a bulk density of 0.43—0.51 g/cm³.

A typical sample of the agglomerates thus-formed has the following particle size distribution:

United States Standard Mesh	Retained
On 60 mesh	—
On 80 mesh	2%
On 100 mesh	14%
On 120 mesh	6%
On 200 mesh	34%
Through 200 mesh	44%

Example 2.

A premix containing sodium ascorbate is prepared by homogeneously blending the following formulation:

Ingredient	Parts by weight
Sodium ascorbate, fine powder	858
Vitamin B_1 mononitrate	20
Vitamin B_2	26
Vitamin B_6	39
Niacinamide	224
Vitamin B_{12} ingredient (0.1% by weight vitamin B_{12})	112
Dextrose	80

Samples of this premix are formed using, as the vitamin B_{12} ingredient, the product prepared as described in Example 1 as well as the commercial gelatin product and the commercial mannitol product which are described hereinbefore. All vitamin B_{12} products tested contain 0.1% by weight of active ingredient. The gelatin product is formed by freezing an aqueous gelatin solution of vitamin B_{12} into sheets and comminuting the sheets to fine particles. The mannitol product is simply an admixture of vitamin B_{12} and mannitol. The premix samples are stored at 45°C for 16 weeks and assayed for percent retention of vitamin B_{12} activity at 8 and 16 week intervals. The results of this test are given in Table I in which the per cent retention activity at 8 weeks is based on the 4 weeks level.

TABLE I

Vitamin B_{12} ingredient	% Retention at 45° C	
	8 weeks	16 weeks
Product of Example 1	90	86
Gelatin product	90	81
Mannitol product	75	65

It will be seen from the foregoing data that the product of Example 1 is more stable than the gelatin product and eminently more stable than the mannitol product in the premix of this Example.

Example 3.

Chewable vitamin tablets are prepared by homogeneously blending the following formulation and directly compressing the blend into tablets:

Ingredient	Amount
Vitamin B_1 mononitrate	1.2 mg
Vitamin B_2	1.5 mg
Vitamin B_6	1.2 mg
Niacinamide	10.0 mg
Vitamin E	2.0 IU
d-Calcium pantothenate	10.0 mg
Vitamin B_{12} ingredient (0.1% vitamin B_{12} by weight)	0.3 mg
Vitamin A acetate	5000.0 Units
Vitamin D_2	400.0 Units
Vitamin C	60.0 mg
Sugar Tab*	*q.s.*
Flavour	*q.s.*

* Direct compression grade modified sucrose, manufactured by Mendell Corp., Yonkers, New York.

Samples of this formulation are prepared using as the vitamin B_{12} ingredient, the product prepared as described in Example 1, as well as the commercial gelatin product referred to hereinbefore (also 0.1% by weight vitamin B_{12}) and compressed into tablets. Samples of these tablets are stored at 45°C for 8 weeks and 12 weeks and also at room temperature for 6 months. The results of these tests are given in Table II.

TABLE II

Vitamin B_{12} ingredient	% Retention at 45° C		% Retention; 6 months at room temp.
	8 weeks	16 weeks	
Product of Example 1	88	90	100
Gelatin Product	87	90	100

The foregoing results establish the excellent stability of the product of Example 1 and show it to be equivalent to the commercial gelatin product in the formulation tested. A composition prepared by the conventional spray-drying of the formulation given in Example 1 and compressing the product into tablets gives results comparable to those given in Table II.

Example 4.

A powdered premix for a soy meal product containing ferrous sulfate is prepared by homogeneously blending the following formulation:

Ingredient	Parts by weight
Magnesium oxide	11.7
Ferrous sulfate	151.7
Vitamin B_1 mononitrate	5.6
Vitamin B_2	5.6
Niacinamide	125.8
Vitamin B_6	11.5
Vitamin B_{12} ingredient	56.2
D-Calcium pantothenate	23.0
Dicalcium phosphate, anhydrous	62.5

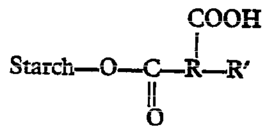
The vitamin B_{12} ingredient is prepared by the conventional spray-drying of the formulation given in Example 1. Samples of the premix are stored at 45°C for 16 weeks (assays are taken at 8 and 16 week intervals) and at room temperature for 3 months. The results of these tests are given in Table III.

TABLE III

Vitamin B_{12} ingredient	% Retention at 45° C		% Retention; 3 months at room temp.
	8 weeks	16 weeks	
Product of Example 1	97	90	97

WHAT WE CLAIM IS:—

1. A stable, dry, free-flowing vitamin B_{12} composition comprising fine particulate vitamin B_{12} coated with a water-soluble, food grade starch derivative of the general formula



(I)

wherein R represents a R′-substituted dimethylene or trimethylene group and R′ represents a hydrophobic group selected from alkyl, alkenyl, aralkyl and aralkenyl groups containing from 5 to 18 carbon atoms.

2. A composition in accordance with claim 1, wherein R represents a substituted dimethylene group.

3. A composition in accordance with claim 1 or claim 2, wherein vitamin B_{12} comprises from 0.05% to 0.5% by weight of said composition.

4. A composition in accordance with claim 1, claim 2 or claim 3, which also contains a non-toxic preservative and a sufficient amount of a buffering agent to buffer the pH of the composition to a pH of from pH 4.0 to pH 4.6.

5. A stable, free-flowing vitamin B_{12} powder composition, which comprises, by weight, about 0.1% of vitamin B_{12}, about 0.1% of sorbic acid, about 0.2% of sodium benzoate, about 10% of a citric acid/sodium citrate buffer sufficient to buffer the pH of said composition to between pH 4.2 and 4.4, from 2% to 3% of silicic acid and, as the remainder, a water-soluble food grade starch derivative of formula I given in claim 1 in which R represents a substituted dimethylene group.

6. A stable vitamin composition in powder form which contains vitamin B_{12} and one or more substances normally deleterious to vitamin B_{12} selected from ascorbic acid, pharmaceutically acceptable salts thereof, iron salts and reducing sugars, wherein the vitamin B_{12} is present in the form of a stable, dry composition as set forth in claim 1.

7. A process for the manufacture of a stable, dry, free-flowing vitamin B_{12} composition as claimed in claim 1, which process comprises spray-drying an aqueous solution of vitamin B_{12} and a water-soluble food grade starch derivative of formula I given in claim 1.

8. A process according to claim 7, wherein a sufficient amount of vitamin B_{12} is present in said solution to constitute from 0.05% to 5.0% by weight of said dry, free-flowing composition.

9. A process according to claim 7 or claim 8, wherein the spray of said aqueous solution is contacted during drying in the spray-dryer chamber with a powder spray of an ultrafine absorbent selected from silicic acid, silicon dioxide, an alkali metal silicate, magnesium carbonate, kaolin clay and dicalcium phosphate.

10. A process according to claim 9, wherein a sufficient amount of said absorbent is added to constitute from 1% to 5% by weight of said dry, free-flowing composition.

11. A process according to any one of claims 7 to 10 inclusive, wherein there is used a starch derivative of formula I in which R represents a substituted dimethylene group.

12. A process for the manufacture of stable, dry, free-flowing vitamin B_{12} compositions, substantially as hereinbefore described with reference to the foregoing Examples.

13. Stable, dry, free-flowing vitamin B_{12} compositions, when manufactured by the process claimed in any one of claims 7 to 12 inclusive.

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